Economics of Malaria Resistance and the Optimal Use of Artemisinin-Based Combination Treatments (ACTs)

Ramanan Laxminarayan

DISEASE CONTROL PRIORITIES PROJECT

DCPP Working Paper No.5

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World Bank • World Health Organization • Fogarty International Center, National Institutes of Health, U.S. Department of Health and Human Services

DISEASE CONTROL PRIORITIES PROJECT

BACKGROUND

In the late 1980s, the World Bank initiated work to inform priorities for control of specific diseases and to generate comparative cost-effectiveness estimates for interventions addressing the full range of conditions important in developing countries. The purpose of the comparative cost-effectiveness work was to provide one input into decision-making within the health sectors of highly resource-constrained countries. This process resulted in the 1993 publication of *Disease Control Priorities in Developing Countries**. A decade after publication of the first edition, the World Bank, the World Health Organization, and the Fogarty International Center (FIC) of the U.S. National Institutes of Health (NIH) have initiated a "Disease Control Priorities Project" (DCPP) that will, among other outcomes, result in a second edition of *Disease Control Priorities* in Developing Countries (DCP*2*). The DCPP is financed in part by a grant from the Bill & Melinda Gates Foundation. DCP*2* is intended both to update DCP*1* and to go beyond it in a number of important ways, e.g. in documentation of success stories, in discussion of institutional and implementation issues, and in explicit discussion of research and development priorities. Publication of DCP*2* is intended for mid-2005.

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Disease Control Priorities Project
Working Paper No. 5

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[1]Ellis McKenzie, Rustom Antia, & Nick White provided useful advice on the epidemiological model. However, they bear no responsibility for remaining omissions.

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Abstract

In the past, malaria control efforts in sub-Saharan Africa have relied on a combination of vector control with effective treatment using chloroquine. With increasing resistance to chloroquine, attention has now turned to alternative treatment strategies to replace this failing drug. Although there are strong theoretical arguments in favor of switching to more expensive artemisinin-based combination treatments (ACTs), the validity of these arguments in the face of financial constraints has not been previously analyzed. In this paper, we use a bioeconomic model of malaria transmission and evolution of drug resistance to examine questions of optimal treatment strategy and coverage when drug resistance places an additional constraint on choices available the policymaker.

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1 Introduction

Recent years have been witness to steady increases in parasite resistance to chloroquine (CQ) in many malaria-endemic countries in sub-Saharan Africa and consequent increases in malaria morbidity and mortality (Trape 2001). The imminent loss of this important drug in the fight against malaria has hampered malaria control efforts and placed greater responsibility on policymakers to rapidly change guidelines to alternative antimalarial treatments, keeping in mind the possibility that these alternatives too could be rendered obsolete by drug resistance. Given the limitations on financial resources in most malaria-endemic countries, there has been a considerable difficulty in deciding on an alternative antimalarial treatment policy to the current chloroquine regimen that is both affordable as well as sound from a long-term perspective. Artemisinin-based combination treatments (ACTs) hold considerable promise of both increased efficacy and retardation in the rate of development of parasite resistance. Although the theoretical basis underlying the epidemiological advantages of artemisinin containing combinations in the treatment of malaria has been studied (Curtis et al. 1986; Hastings et al. 2000; White 1999; White 1998), there has been little attention paid to the economic desirability of using ACTs. The focus of this paper is on the economic evaluation of alternatives to the current chloroquine guidelines, and the implications for the allocation of scarce financial resources for malaria treatment, when future resistance is a consideration.

In response to growing resistance to CQ, many countries have considered changing their official guidelines for first line treatment either to sulfadoxine-pyrimethamine (SP) or ACTs. SP offers distinct advantages over ACTs in that it costs roughly a tenth that of ACTs per treatment dose, is administered as a single treatment and is approved for use in

children and pregnant women[2]. An important drawback with switching to SP, however, is that it is expected that resistance will increase with widespread use and may leave policymakers with a similar situation of growing malaria morbidity and mortality a few years from now (Winstanley 2000). An alternative strategy would be to switch to ACTs immediately. ACTs offer the advantage of delaying resistance for much longer time period than SP while offering faster cure rates. However, there is some concern about whether ACTs would actually work to delay resistance in sub-Saharan Africa where there is poor adherence to treatments and underdosing among other concerns (Bloland et al. 2000). Furthermore, there is uncertainty about the benefits of ACTs when there is potential for use of one of drugs in the combination as monotherapy.

In this paper, we develop a mathematical, bioeconomic model of malaria transmission, immunity and drug resistance. The model is then applied to addressing two specific questions. First, we compare the economic consequences of two strategies, the first of which involves replacing CQ with ACTs, and the second of which involves replacing CQ with SP, waiting for resistance to develop before introducing ACTs. The second question addressed in this paper pertains to the optimal level of coverage using ACTs. Here one is faced with the constraint that while increasing access to an effective antimalarial in any given region or location both lowers morbidity and saves lives, it involves economic costs and an increasing likelihood that resistance will develop to the drug being used. Furthermore, policy makers may have decide whether to devote all their resources to increasing treatment coverage in a few regions or to distribute these resources over a number of regions.

2 Mathematical Model

The use of antimalarials involves costs and benefits that occur at different points in time. On the one hand, using effective antimalarials in the present benefits society by lowering the current economic burden of malaria morbidity. On the other hand, expanding the use of antimalarials

[2]There is substantial disagreement over the cost of ACTs and current estimates vary between $1.00 per adult dose (Médecins Sans Frontières) and $2.50 for artemether-lumafantrine at the WHO negotiated price for developing countries. It is likely that with widespread adoption of new ACTs, the price will drop significantly and the lower bound estimate of $1.00 would be a reasonable approximation of the long run marginal cost of these treatments. The current price for SP is roughly $0.12 per dose

while increasing the cost of treatments potentially increases the likelihood that resistance will evolve which in turn could lead to greater morbidity in the future. Converting present and future morbidities into economic metrics permits a consistent comparison of different strategies for antimalarial use over the policymaker's planning horizon.

The policymaker's objective is to inter-temporally minimize the sum of discounted present value of costs of infection and the cost of treatment. This objective is constrained by the biology of the disease as reflected by the dynamics of malaria transmission and evolution of drug resistance. Disease dynamics are modeled using a compartmental model where individuals move between healthy (susceptible), infected and immune classes. Although factors such as age structure, degree of parasitemia, latency and genetic variability play an important role in malaria dynamics, the model presented is abstracted from these secondary considerations to focus sharply on the role of treatment in malaria transmission, and the evolution of resistance and immunity. Malaria transmission is assumed to be year-round and stable. Superinfections are ruled out, although this may make a quantitative difference in terms of increasing infection rates (Anderson et al. 1991).

Biology

We follow the basic mathematical model of malaria described in Koella (1991) and earlier papers (Aron 1988a; Aron 1988b), modified to incorporate the evolution of resistance (see Figure 1 for schematic)[3]. As in previous literature in this area, we assume that the mosquito dynamics operate on a much faster time-scale than the human dynamics, so that the mosquito population can be considered to be at equilibrium with respect to changes in the human population, and its dynamics can be collapsed into the inoculation rate (Koella 1991). The inoculation coefficients are given by

$$h_w = ma^2 b_1 b_2 e^{-\mu T} \frac{y_w}{a + \mu y_w}$$ and $$h_r = ma^2 b_1 b_2 e^{-\mu T} \frac{y_r}{a + \mu y_r}$$ for wild-type resistant

[3]Since this paper was completed, a new paper published by Koella and Antia that incorporates resistance into a model of malaria transmission has been brought to my attention Koella J, Antia R. Epidemiological models for the spread of anti-malarial resistance. Malar J 2003; 2 (1):3. Their model differs only in minor respects to the one developed in this paper.

strains respectively. a is the biting rate (number of bites per female mosquito per night), b_1 is the infectiousness of humans to mosquitoes, b_2 is the susceptibility of mosquitoes to humans, m is the mosquito density (number of mosquitoes per human), τ is the incubation period of parasites in the mosquito, and μ is the mortality of mosquitoes. y denotes the proportion of infected individuals in the human population (see equations below), y_m is the fraction of infected patients with a susceptible strain, and y_r carry a resistant strain ($y_w + y_r = y$). Let the proportions of susceptibles and immunes be denoted by x and y so that $x + y_w + y_r + z = 1$. The differential equations that describe changes in the classes of susceptibles, infecteds (wild-type or sensitive strain), infecteds (resistant strain) and immunes are,

(1) $$\dot{x} = \delta + my - \delta x - x\left(h_w y_w + h_r y_r\right) + \gamma z + f\alpha y_w$$

(2) $$\dot{y}_w = h_w x - \left(\theta_w + \delta\right) y_w - f\alpha y_w$$

(3) $$\dot{y}_r = h_r x - \left(\theta_r + \delta\right) y_r$$

(4) $$\dot{z} = \theta\left(y_w + y_r\right) - \left(\gamma + \delta\right) z$$

Susceptibles become infected with a sensitive parasite at a rate h_w, the inoculation rate for sensitives, and with a resistant parasite at a rate h_r defined earlier.[4,5] Individuals with a wild-type strain recover at a rate θ_w to enter the immune class, while individuals with a resistant strain recover at a rate $_r$. The spontaneous rate of recovery from the resistant infection is assumed to be greater than that for sensitive infections;

[4]Interventions such as impregnated bednet use will likely reduce this transmission coefficient. Although the use of ACT is expected to reduce gametocyte carriage and hence parasite transmissions, we shall assume that ACT reduces transmission primarily by curing patients more rapidly.

[5]One strand of the mathematical epidemiology literature on malaria resistance focuses on the relative importance of transmission rates on evolution of drug resistance Mackinnon MJ. Survival probability of drug resistant mutants in malaria parasites. Proc. R. Soc. Lond. B. 1997; 264:53-9, Mackinnon MJ, Hastings IM. The evolution of multiple drug resistance in malaria parasites. Transactions of The Royal Society of Tropical Medicine and Hygiene 1998; 92:188-95.. According to one camp, high transmission results in higher recombination breakdown if resistance is coded for by more than one locus. The other camp holds that drug selection pressure is the more powerful force; therefore, higher transmission rates leads to increased resistance. The model implicitly adheres to the latter argument.

hence $_r \geq \ _w$. The difference between these rates represents the treatment fitness cost of resistance[6]. Immunes become susceptible again at a rate γ. Transmission fitness cost of resistance is assumed to be negligible[7]. Births equal deaths, so population size remains unchanged.

f is the fraction of the infected population that receives treatment. Infected individuals who are treated successfully (because they carry a sensitive parasite) return to the susceptible state. There is some evidence that the benefit of effective treatment is accompanied by a loss of immunity (Cornille-Brogger et al. 1978; Pringle et al. 1966). Treatment, therefore, discourages expansion of the immune class. The use of ACTs or some similar effective treatment strategy does not alter transmission intensity in this model, but reduces the number of circulating parasites by reducing the duration of illness.

The reproductive number of susceptible and resistant parasites is given by $R_w = \frac{ma^2 b_1 b_2 e^{-\mu T}}{(\theta_w + \delta + f\alpha)\mu}$ and $R_r = \frac{ma^2 b_1 b_2 e^{-\mu T}}{(\theta_r + \delta)\mu}$ respectively.

The ratio of reproductive numbers is $\frac{R_r}{R_w} = \frac{\theta_w + \delta + f\alpha}{\theta_r + \delta}$.

Increasing treatment coverage increases this ratio. At f = 0.5, this ratio is equal to 3 for the parameter values used in our model. The critical coverage at which there is no growth in resistance is given by $f_c = \frac{(\theta_r - \theta_w)}{\alpha}$, which is roughly 0.12 for the parameter values used in our model. In any period, the fraction of malarial parasites that are resistant to the drug, r, is defined as

(5) $r = \frac{y_r}{y_r + y_w}$

[6]For a discussion of the fitness cost of resistance, see Koella JC. Costs and benefits of resistance against antimalarial drugs. Parasitology Today 1998; 14 (9):360-64.

[7]It is possible that resistant parasites are less likely to be transmitted from humans to mosquitoes and back and this places them at an evolutionary disadvantage with respect to sensitive parasites.

Economics

A number of studies have examined the direct and indirect costs of an episode of malaria (Chima et al. 2003; Ettling et al. 1994; Ettling et al. 1991a; Ettling et al. 1991b; Sauerborn et al. 1991). However, these costs tend to be highly context and location-specific with limited generalizability to other settings (Gomes 1993). A range of cost estimates for morbidity and treatment are drawn from the existing literature to allow a sensitivity analysis based on variations in the cost parameters.

Estimates of lost work time ranges from one to five days. In general, indirect costs associated with lost productive labor time account for a relatively large fraction of overall costs of malaria. For instance, a study that surveyed 1614 households in rural Ghana found that the average direct cost of treating malaria which included cost of drugs, consultation, laboratory service and transportation constituted roughly 20% of the cost of treatment. Indirect costs that measured the opportunity cost of travel, time, waiting and loss of productive time made up the remaining 80% (Asenso-Okyere et al. 1997). Another study that compared malaria related costs in four sites in Africa (in Rwanda, Burkina Faso, Chad and Congo) found that on average, a case of malaria cost $1.83 (1987 $) in direct costs (treatment expenditure and control) and $9.84 in indirect costs (morbidity, mortality and economic losses) (Shepard et al. 1991). In all sites, the indirect costs were much greater than the direct costs and typically accounted for roughly 90% of total costs (excluding quality of life costs). These studies indicate that the cost of drug treatment may only be small percentage of the overall costs of treating malaria.

For the purpose of our simulations we assume a morbidity cost of $0.50 per infected patient per day. In the base case the cost of a dose of SP was assumed to be $0.12 and cost of ACTs was assumed to be $1.00. Non-drug treatment costs were assumed to be zero. However, including the cost of treatment favors the strategy of introducing ACTs immediately since the cost of the drug may not add substantially in percentage terms to the costs associated with malaria. Finally, all costs were discounted at a constant, annual rate of 3%.

Analysis

Present discounted cost of treatment and infection for different levels of coverage were computed and compared for two treatment strategies. In strategy A, ACTs were introduced immediately and resistance was allowed to evolve as an increasing function of treatment coverage. In strategy B, SP was introduced at time 0 and resistance was allowed to evolve to 20% at which point the treatment was switched to ACTs. The resistance switch point was selected arbitrarily and one could well make a case for it being higher or lower. The switch point was varied to 40% in the sensitivity analysis.

Computations were made for a base population of 1 million. In order to focus on the cost of ACTs and the optimal levels of coverage based on treatment and infection costs, we made the simplifying assumption that those who do not receive ACTs take chloroquine or some other drug which does not compromise the long term efficacy of the combination treatment. If this assumption were to be relaxed, we find that we may be worse off with very low levels of ACTs coverage (relative to coverage with monotherapy with either drug in combination) than with no ACT use at all. Furthermore, the success of ACTs would depend largely on reducing use of the artemisinin derivative's partner drug in monotherapy. Malaria-specific mortality was assumed to be zero although introducing an appropriate case-fatality rate did not alter any of the results qualitatively.

Model parameters are summarized in Table 1. In addition, we have conducted extensive sensitivity analyses around these point estimates, some of which are described in the following section.

3 **Results**

Since the parameter values used in the simulations were intended to broadly representative of the situation in sub-Saharan Africa and are not precisely applicable to any single context, it is probably more useful to focus on the qualitative results and orders of magnitude indicated rather than on the numbers themselves.

Figure 2 plots the infection rates and resistance for three levels of coverage (20%, 40% and 60%) over three time horizons; five, ten and twenty years, to represent the short, medium and long term. Infection rates initially decline in response to the introduction of the effective drug to replace chloroquine, but increase with increasing resistance. In the longer term, they decline with the increase of immunity to the parasite. The increase of parasite resistance follows the familiar logistic function. The third plot describes the present discounted cost of treatment and infection for three different levels of coverage with an effective treatment such as combination treatment. Higher levels of treatment coverage shifted the cumulative discounted cost curve downwards.

Figure 3 plots the present discounted value of treatment and infection costs for Strategy A under the base case parameter values over three time horizons; five, ten and twenty years, to represent the short, medium and long term. Costs of infection declined for increasing levels of coverage but at a declining rate. Treatment costs increased linearly with treatment coverage. Even at high levels of coverage, treatment costs represent only a small proportion (roughly 5%) of the economic costs associated with malaria morbidity.

The same graph is repeated for Strategy B where SP was introduced to replace CQ, in Figure 4. Here too, the costs of malaria morbidity were declining with increasing treatment coverage even after resistance related impacts on future morbidity were taken into consideration. Figure 5 displays the difference in costs between strategies A and B. A positive value implies that Strategy B is more costly than strategy A. Strategy B was preferred at both very low levels of coverage and high levels of coverage, but strategy A was preferred for coverage fractions ranging from 0.2-0.8 for a 20 year policymaking horizon. Broadly speaking, strategy B was the preferred option for a time horizon of 5 years, while strategy A was preferred if the policymaker's planning horizon extends to 10 or 15 years. For a 40% level of treatment coverage, strategy A resulted in roughly $6 million less present discounted costs for the 10 and 20 year time horizons, while strategy B resulted in roughly $0.8 million less in present discounted costs over the 5 year horizon.

When the cost of ACTs per treatment dose was increased from $1 to $2 in a sensitivity analysis, the cost of strategy A increased to a greater extent for all levels of treatment coverage (Figure 6). However, the impact on overall costs differences between the two strategies remained unchanged. When the level of resistance at which a switch from SP to ACT was made in strategy B was changed from 20% in the base case to 60%, the relative advantage of strategy A declined for coverage below 0.5 for longer treatment horizons but increased for coverage above 0.5 (Figure 7). In a third sensitivity analysis, the discount rate was increased to 6% from the base case value of 3% (Figure 8). This resulted in an improvement from the base case for shorter time horizons. However, for longer time horizons, the cost advantage of strategy A was smaller relative to the base case. Finally, the value of R_0 was increased from 100 in the base case to 300 to capture settings of more intensive transmission (Figure 9). This variation did not make a significant difference to the relative costs of strategies A and B from the base case.

4 Discussion

Artemisinin-based combination therapies (ACTs) that combine an artemisinin derivative with another antimalarial such as piperaquine or amodiaquine promise both increased efficacy, and a reduction in the rate of development of resistance. Additionally, ACTs may help reduce malaria transmission, which in low transmission settings would reduce the incidence of malaria. The current policy debate centers around whether malaria endemic countries that face high disease burdens, due in part to increasing chloroquine resistance should switch to ACTs which are much more expensive than current drugs. If these countries were to switch to SP as an interim measure, this would delay the higher treatment cost of ACTs. The downside of the interim measure, however, is that resistance to SP is expected to rise in a few years leading to increased morbidity and mortality.

Our analysis shows that total discounted costs of infection are decreasing with increasing levels of coverage with either strategy. This is attributable to faster cure rates, lower morbidity and consequently and fewer secondary infections. Further, discounted costs of infections decline more rapidly with treatment coverage for low levels of coverage. After reaching

a roughly 50% level of coverage, the decline in costs is no longer as dramatic, primarily because the increased risk of resistance developing in an area through higher coverage weight against the benefits of treating more patients.

We find that switching to SP first may be preferable at both very low and very high levels of treatment coverage. At very low levels of treatment coverage and low selection pressure, resistance to SP is not a problem and so the least expensive drug is preferred. At high levels of treatment coverage, resistance evolves so rapidly regardless of which strategy is followed that the faster acquisition of immunity with an ineffective drug plays a critical role in determining the superior strategy. We find that for shorter time horizons, it may be economically desirable to switch to SP first to delay the costs of ACTs. If one were only interested in the short term, then using the less expensive drug makes better economic sense since the costs of resistance related morbidity do not enter the policymaker's set of considerations. However, for longer planning horizons, a direct switch to ACTs may be desirable given the costs of higher morbidity associated with increasing resistance to SP. With higher intensity of disease transmission, the benefit of switching to ACTs directly is diminished because of greater immunity associated with higher transmission, and hence a lower risk of resistance developing to SP monotherapy. Resistance to SP would be expected to take longer to develop and therefore, the benefits of switching to SP first increase.

Altering the cutoff level of SP resistance for the change in strategy B from 20% to 60% does not change the difference in costs between the two strategies significantly. Increasing the discount rate places more weight on current costs and benefits compared to those that occur in the future. This reduces the value to introducing ACTs since future resistance-related morbidity costs play a smaller role in the policy decision and therefore, it makes sense to introduce the cheaper drug (SP) initially.

If countries could easily switch between drugs, then it would make sense to introduce the cheaper drug (SP) first, and move to ACTs before resistance to SP has much impact on malaria morbidity. However, this is not likely to happen for two reasons. First, malaria-endemic countries

have shown great reluctance to modify their malaria treatment policies proactively in response to impending resistance related morbidity. The fact that CQ is being used even with high treatment failure rates when an alternative drug (SP) is available is emblematic of policy failures in health decision-making. Second, the costs of each change of treatment policy may be large, for which reason a direct switch to ACTs may be preferred. These policy change costs are associated with retraining of health workers, cost of printed material explaining new dosing regimes, restocking of new drugs and so forth and can account for significant costs in the short term. In the case of a switch to SP, these policy change costs will have to be amortized over a much shorter life of the drug, than in the case of a switch to ACTs. Our analysis, which does not incorporate these policy change costs therefore errs on the side of being conservative with regard to cost advantages of a direct switch to ACTs.

There are other considerations that play an important role in the selection of the most appropriate antimalarial treatment strategy. First, an important parameter that determines the evolution of resistance to ACTs is the starting frequency of resistance, not just to artemisinin but also to the partner drug in the combination. With the widespread availability of all antimalarials from private drug sellers in Africa, it may be difficult to control the emergence of resistance to the companion drug, which in turn would expedite the emergence of resistance to the combination. Our model shows that the economic advantages of introducing ACTs immediately are generally lower for higher starting frequencies of resistance to either drug in the combination, although this result depends on the impact of effective treatment on retarding the acquisition of immunity. Second, SP involves a one day treatment dose, which is much easier to comply with than the five day treatment of ACTs. To the extent that reduced compliance, which is more likely in the case of ACTs will significantly expedite the evolution of resistance, our analysis errs on the side of overstating the economic advantages of immediate introduction of ACTs.

Our analysis also indicates that there may be decreasing returns to treatment coverage. Given the tight constraints placed on malaria treatment resources in sub-Saharan Africa, it may be economically efficient to maximize availability of antimalarials in all areas rather than focusing resources on just a few areas. However, other factors such as scale economies in treatments may also play a role and work in the opposite direction.

In spite of evidence of significant societal benefits of ACTs, policymakers are likely to be deterred by the immediate cost of ACTs and the burden that adopting a more expensive drug would place on their already overextended health budgets. However, the real choice is not about whether or not to use ACTs but whether to introduce them now, or to delay their introduction for a few years while SP could be used. This situation could change with the introduction of new and improved antimalarials, but the prognosis for this happening is bleak. Ultimately, it is the planner's time horizon that will play an important role in naming a successor to chloroquine.

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Figure 1
Model of disease transmission

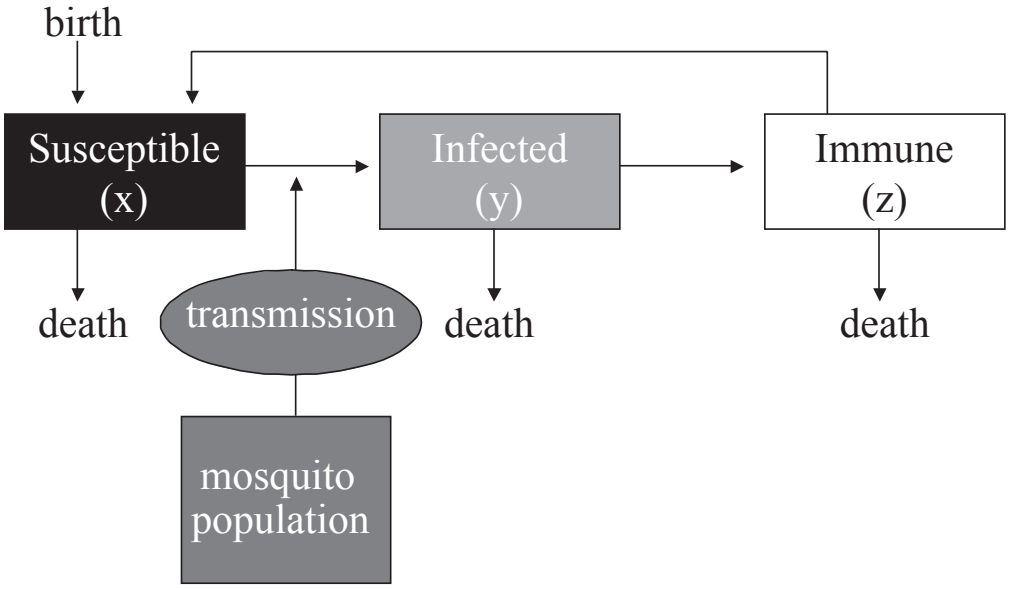


Table 1
Parameter values for simulations

Symbol	Description	Value (range for sensitivity analysis)
a	Biting rate (number of bites per female mosquito per night)	100 per year
b_1	Infectiousness of humans to mosquitoes	0.8
b_2	Infectiousness of mosquitoes to humans	0.8
m	Mosquito density	10
μ	Mosquito mortality rate	3 per month
$_w$	Spontaneous rate of recovery of infected susceptible individuals	0.7/year
$_r$	Spontaneous rate of recovery of infected resistant individuals	2.4/year
α	Excess rate of recovery of treated individuals	12/year
τ	Incubation period of parasites in mosquito	10 days
γ	Rate of loss of immunity	0.1/year

Source: Koella (1991)

Figure 2
Time path of infections, parasite resistance and cumulative discounted costs for different levels of treatment coverage

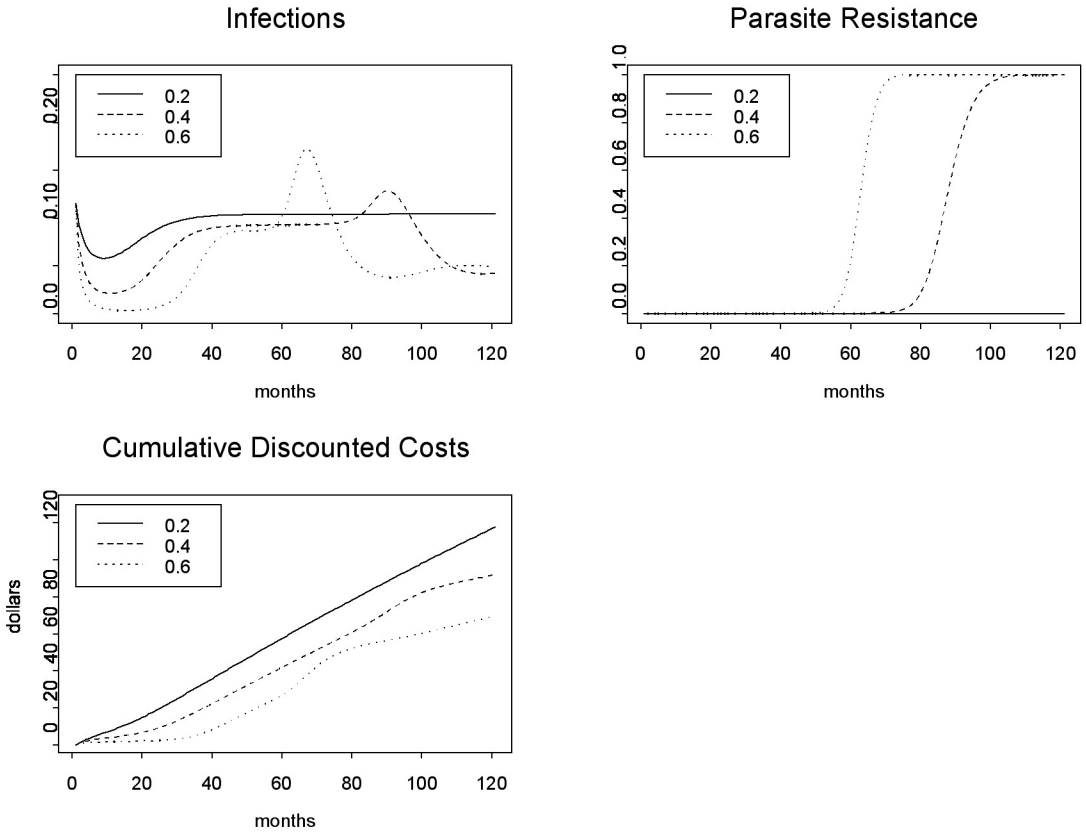


Figure 3

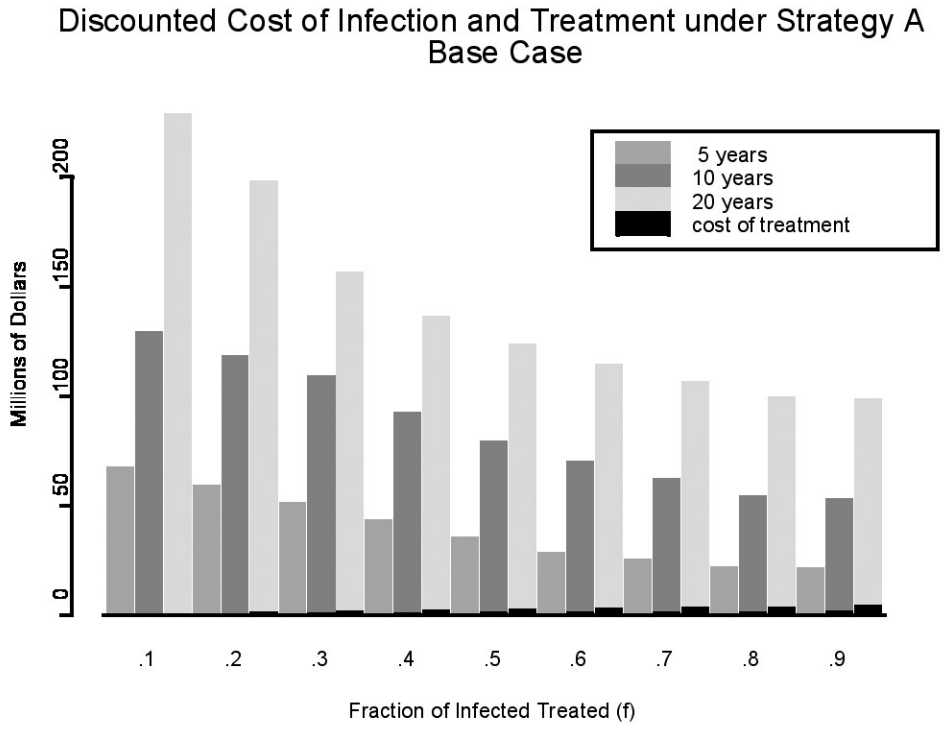

Discounted Cost of Infection and Treatment under Strategy A
Base Case
5 years
10 years
20 years
cost of treatment
Millions of Dollars
0
50
100
150
200
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 4

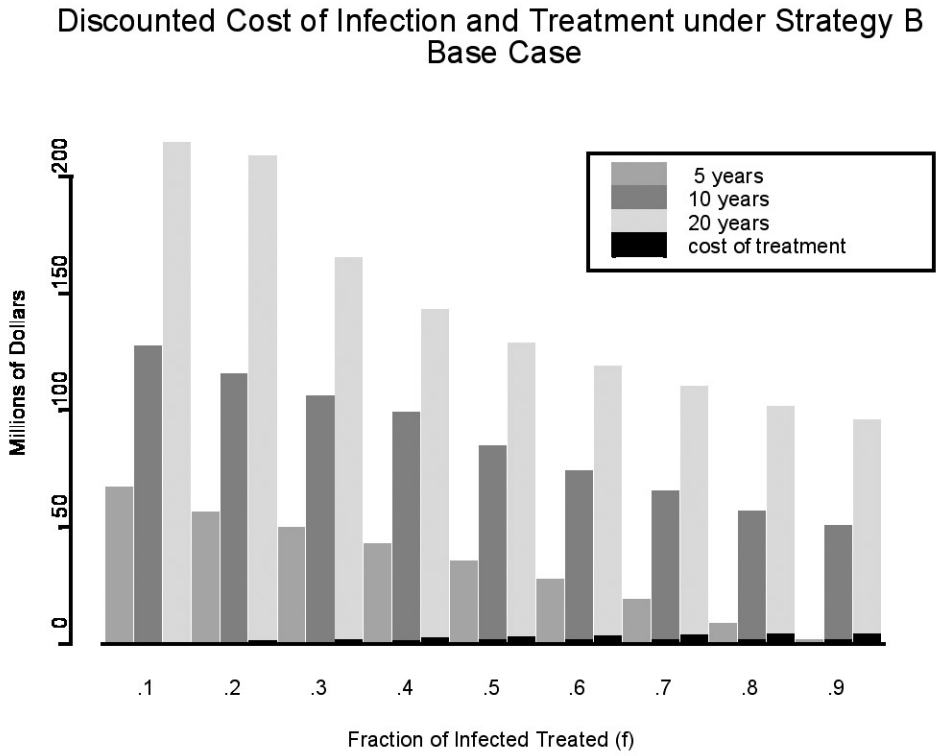

Discounted Cost of Infection and Treatment under Strategy B
Base Case
5 years
10 years
20 years
cost of treatment
Millions of Dollars
0
50
100
150
200
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 5

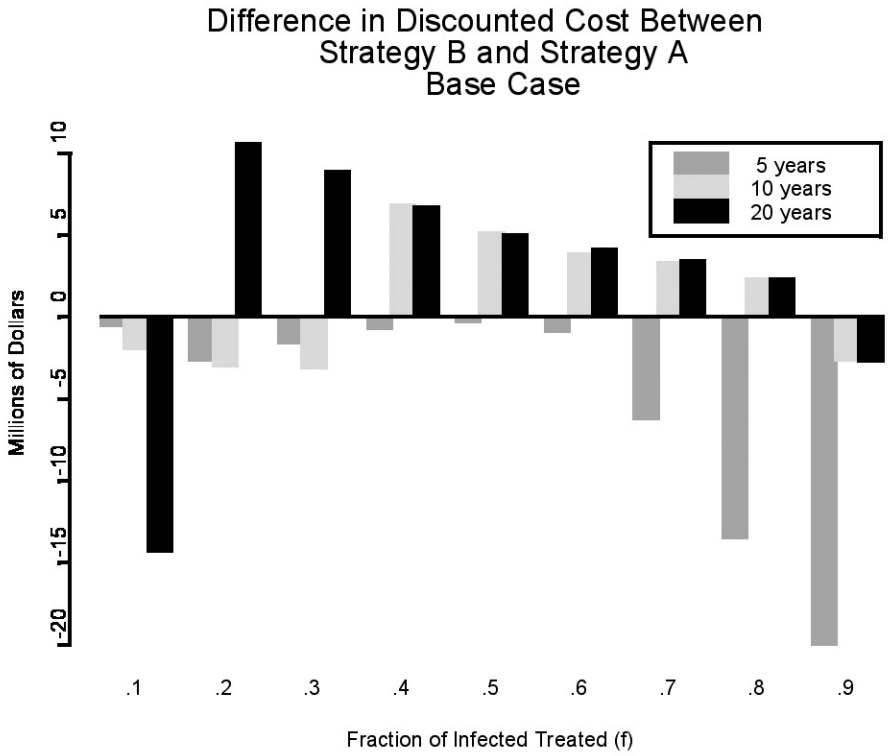

Difference in Discounted Cost Between
Strategy B and Strategy A
Base Case
5 years
10 years
20 years
Millions of Dollars
10
5
0
-5
-10
-15
-20
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 6

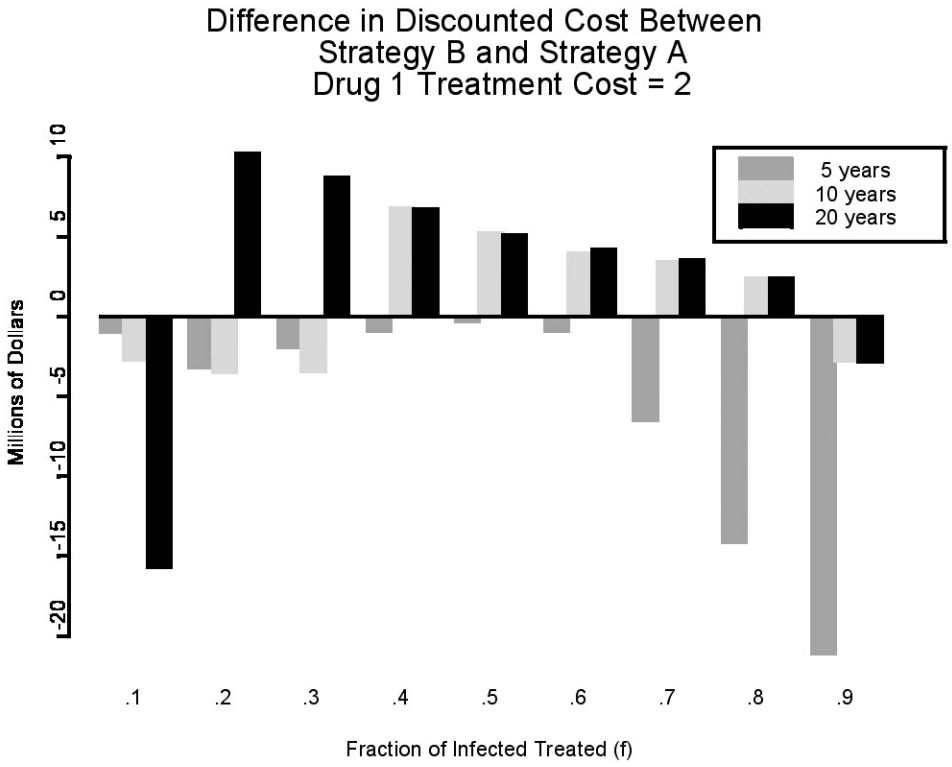

Difference in Discounted Cost Between
Strategy B and Strategy A
Drug 1 Treatment Cost = 2
5 years
10 years
20 years
Millions of Dollars
10
5
0
-5
-10
-15
-20
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 7

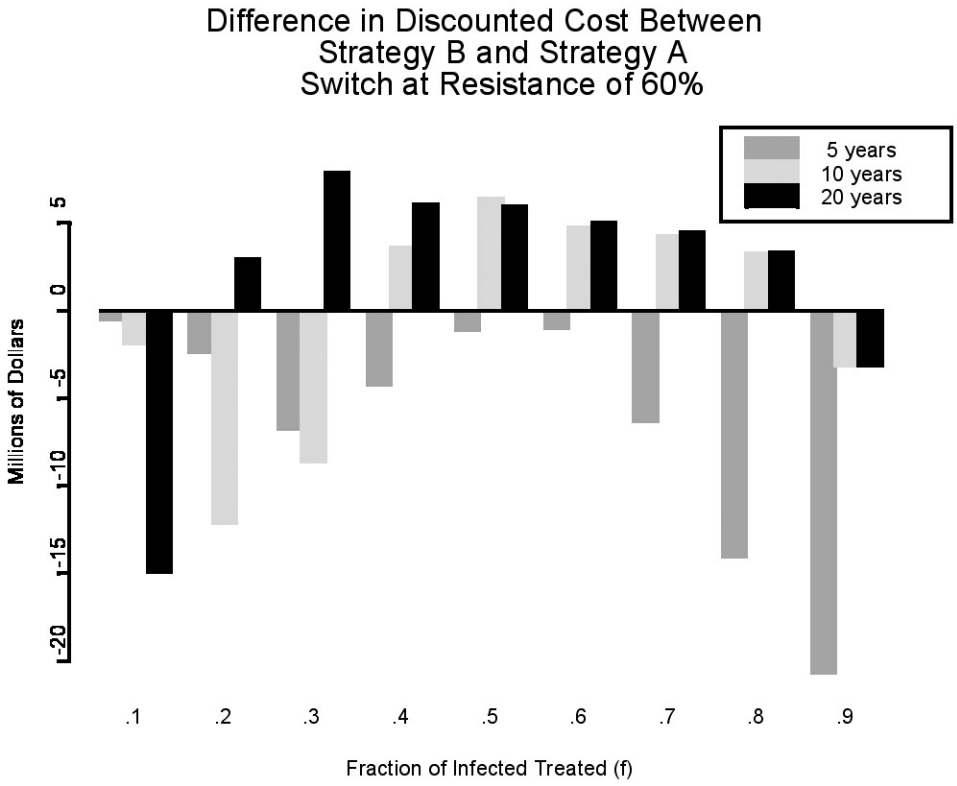

Difference in Discounted Cost Between
Strategy B and Strategy A
Switch at Resistance of 60%
5 years
10 years
20 years
Millions of Dollars
5
0
-5
-10
-15
-20
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 8

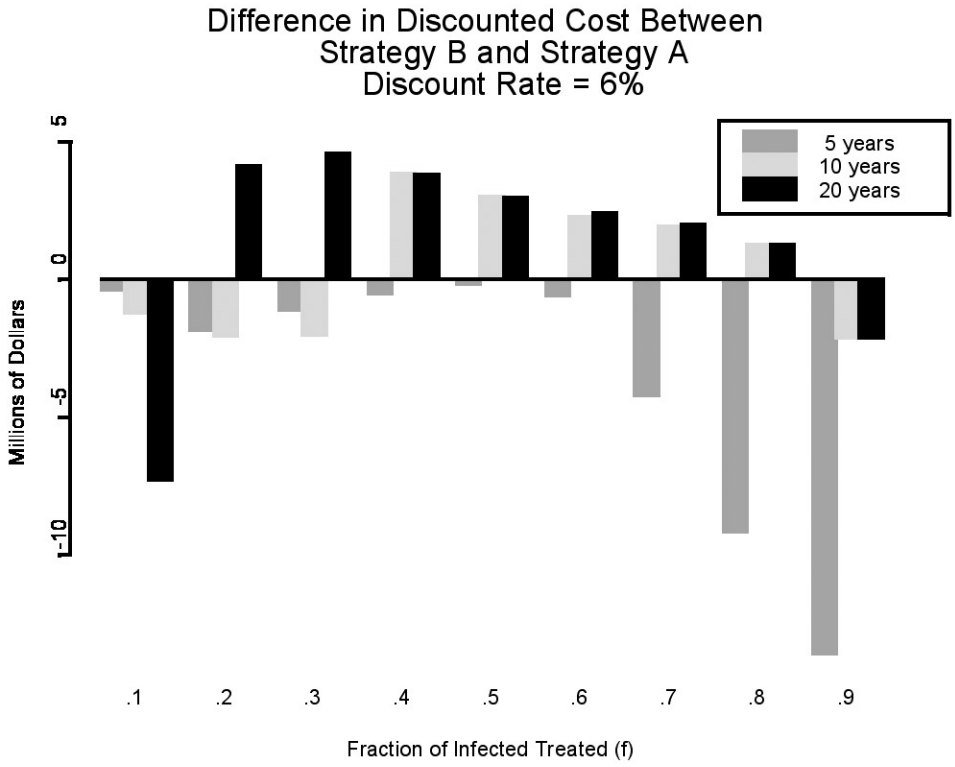
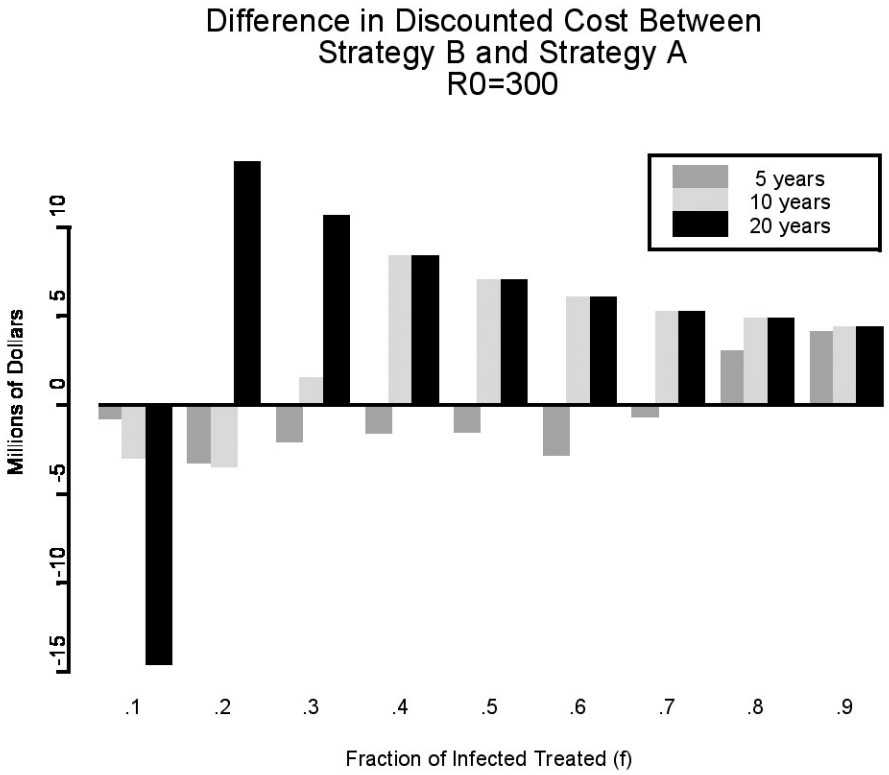

Difference in Discounted Cost Between
Strategy B and Strategy A
Discount Rate = 6%
5 years
10 years
20 years
Millions of Dollars
5
0
-5
-10
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

Figure 9


Difference in Discounted Cost Between
Strategy B and Strategy A
R0=300
5 years
10 years
20 years
Millions of Dollars
10
5
0
-5
-10
-15
.1
.2
.3
.4
.5
.6
.7
.8
.9
Fraction of Infected Treated (f)

DCPP Working Papers

1. At Least One-Third Of Poor Countries' Disease Burden Is Due To Malnutrition. By John B. Mason, Philip Musgrove and Jean-Pierre Habicht. March 2003.

2. Progress In The Development Of A Recombinant Vaccine For Human Hookworm Disease: The Human Hookworm Vaccine Initiative. By Peter J. Hotez, Bin Zhan, Jeffrey M. Bethony, Alex Loukas, Angela Williamson, Gaddam Narsa Goud, John M. Hawdon, Azra Dobardzic, Reshad Zook, Yan Wang, Sen Liu, Idong Essiet-Gibson, Sophia Chung-Debose, Shushua Xiao, David Knox, Michael Meagherf, Mehmet Inan, Rodrigo Correa-Oliveira, Paul Vilk, Herman R. Shephard, Walter Brandt, and Philip K. Russell. March 2003.

3. Soil Transmitted Helminth Infections: The Nature, Causes And Burden Of The Condition. By Peter J. Hotez, Nilanthi de Silva, Simon Brooker and Jeffrey Bethony. March 2003.

4. Discounting. By Dean T. Jamison and Julian S. Jamison. March 2003.

5. Economics of Malaria Resistance and the Optimal Use of Artemisinin-Based Combination Treatments (ACTs). Ramanan Laxminarayan. July 2003.

6. Do Malaria Control Interventions Reach the Poor? A View Through the Equity Lens. Lawrence Barat, Suprotik Basu, Eve Worrall, Kara Hanson, Anne Mills. July 2003.

7. New Perspectives on the Causes and Potential Costs of Malaria: The Growth and Development of Children. What Should We Be Measuring and How Should We Be Measuring It? Penny Holding, P.K. Kitsao-Wekulo. July 2003.

8. Pediatric Anemia and Mortality in Africa: Plasmodium falciparum Malaria as a Cause or Risk? Robert W.Snow, Eline L. Korenromp, Chris Drakeley, Eleanor Gouws. July 2003.

9. Unit Prices of Health Care Inputs in Low and Middle Income Regions: An outline and discussion of data for use in DCPP chapters. Mulligan J, Fox-Rushby J, Mills A. August 2003.

10. Health's Contribution to Economic Growth in an Environment of Partially Endogenous Technical Progress. Dean T. Jamison, Lawrence J. Lau, Jia Wang. July 2003

11. The Public Health of Plasmodium falciparum Malaria in Africa: Deriving the Numbers. By Robert W. Snow, Marlies H. Craig, Charles R.J.C. Newton, and Richard W. Steketee. Working Paper No. 11, Disease Control Priorities Project. Bethesda, Maryland: Fogerty International Center, National Institutes of Health. September 2003.

12. Soil-Transmitted Helminth Infections: Updating the Global Picture. By Nilanthi de Silva, Simon Brooker, Peter Hotez, Antonio Montresor, Dirk Engels, and Lorenzo Savioli. Working Paper No. 12, Disease Control Priorities Project. Bethesda, Maryland: Fogerty International Center, National Institutes of Health. September 2003.

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